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TOWNSEND and TOWNSEND and CREW LLP

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PATENT
Attorney Docket No.: 02558B-063700US
Client Ref. No.: BRP00107

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**BOARD OF PATENT APPEALS AND INTERFERENCES**

| | |
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| In re application of: | Confirmation No. 3942 |
| Steven R. Binder | Examiner: Marianne P. Allen |
| Application No.: 09/691,405 | Technology Center/Art Unit: 1647 |
| Filed: October 17, 2000 | APPEAL BRIEF UNDER 37 CFR §§41.31 and 41.37 |
| For: PATTERN RECOGNITION METHOD FOR DIAGNOSIS OF SYSTEMIC AUTOIMMUNE DISEASES | |
| Customer No.: 20350 | |

**Mail Stop Appeal Brief**
Commissioner for Patents
Board of Patent Appeals and Interferences
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant hereby submits this appeal brief pursuant to 37 CFR §41.37. A return receipt postcard received by appellant indicates that the date of receipt by the Patent Office of appellant's notice of appeal is July 10, 2006. Thus, pursuant to 37 CFR §41.37(a), this Appeal Brief was due on August 10, 2006, extensions of time being permitted. Accordingly, Appellants request a three month extension of time to extend the due date to November 13, 2006 (with Friday, November 10, 2006 being a Federal Holiday). The Commissioner is hereby authorized to charge deposit account no. 20-1430.

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**REAL PARTY IN INTEREST:**

The real party in interest of the subject patent application is Bio-Rad Laboratories, Inc., the owner of the patent application.

**RELATED APPEALS AND INTERFERENCES:**

There are no known related appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

**STATUS OF CLAIMS:**

Claims 1, 2, 5-10, and 12-20 are pending. Claims 1-2, 5-10 and 12-20 stand rejected. Appellants appeal from the rejection of claims 1-2, 5-10, and 12-20.

**STATUS OF AMENDMENTS:**

No amendments have been filed subsequent to receipt of the final Office Action mailed on January 20, 2006, which has necessitated this Appeal.

**SUMMARY OF THE CLAIMED SUBJECT MATTER:**

Embodiments of he present invention relate to a computer-implemented method of identifying whether a test subject may be suffering from one or more systemic autoimmune diseases (SADs) by comparing a test data set for a test subject (e.g., patient) with a plurality of stored reference data sets derived from reference subjects, each known to be afflicted by none, one or more particular SADs. The present invention may be used in a computer based system such as a medical decision support system. See, e.g., page 3, lines 14-19 and page 6, line 32 to page 7, line 2. The patient data set and each reference data set are obtained by subjecting a biological sample to a set of one or more tests; each data set includes values representing levels of a plurality of autoantibodies as determined by the same set of one or more tests. The reference data sets are stored, e.g., to a database, for comparison with test data sets for patients. The reference data sets include data sets for reference samples taken from subjects that have disease conditions that are known, and data sets for reference samples taken from subjects that are known to be disease free. Each reference data set may be labeled (in a database) as to the particular disease it is associated with. The patient data set is compared with the reference data sets by applying a k-nearest neighbor (KNN) process, or algorithm. The KNN process effectively processes the reference data sets and patient data set as data points in an N-dimensional space, where N is the number of test values (e.g., antibody test levels) obtained for each sample (see, e.g., page 4, lines 21 to 29) from the set of tests. The disease(s) associated with the k nearest reference data points that are closest to the test data point (based on a numeric distance metric) is identified as a likely disease which is present in the patient sample from which the patient data point is derived. If the k nearest data points are associated with more than one disease, the diagnosis for each of the diseases may be indicated. If the k nearest data points are associated with none of the diseases (e.g., if many or all of the k nearest reference data points were derived from subjects known to be disease free), then the diagnosis would be "none". The identified SADs may be used by a diagnosing physician to assist with a diagnosis of the patient.

In one embodiment, for example, as recited in claim 1, the present invention provides a method for identifying whether a test subject is suffering from one or more SADs selected from the group consisting of systemic lupus erythmatosus, scleroderma, Sjögren's syndrome, polymyositis, dermatomyositis, CREST, and mixed connective tissue disease (e.g., page 10, lines 14-19). The method typically includes receiving a test data set for the test subject (e.g., patient), wherein the test data set is obtained by subjecting a biological sample of the test subject to a set of one or more tests that produce values representing levels of a plurality of autoantibodies present in the sample (see, e.g., page 4, line 30 to page 5, line 5; page 4, lines 15 to 19, and page 10, lines 10 to 14). The method also typically includes storing a plurality of reference data sets including i) reference data sets obtained for each of said one or more SADs by subjecting biological samples of reference subjects, each known to have one of said one or more SADs, to said set of one or more tests, and ii) reference data sets obtained by subjecting biological samples of reference subjects known to not have one of said one or more SADs to said set of one or more tests (e.g., page 4, lines 10-15; and page 5, lines 1 to 5). Each stored reference data set is derived from a sample that has been subjected to the same set of tests as the both the test subject sample and the other reference samples (see, e.g., at page 4, lines 11 to 16; page 5, lines 1 to 5). The method also includes comparing the test data set and the stored reference data sets by applying a k-nearest neighbor algorithm to produce a statistically derived decision indicating whether the test subject is suffering from none, one or more of said SADs (e.g., page 5, lines 6-8 and 14-22). The method further includes identifying which of said SADs the test subject is suffering from if the statistically derived decision indicates that the test subject is suffering from one or more of said SADs (e.g., page 5, lines 19-22). A physician may use the statistically derived decision, for example, to assist with a diagnosis and/or request additional testing.

**GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL:**

The issues on appeal are:

Whether claims 1, 2, 5-10, and 12-20 are unpatentable under 35 USC §112, first paragraph, for lack of enablement.

## ARGUMENT

### I. Rejection under 35 USC §112, first paragraph, for lack of enablement

Claims 1, 2, 5-10, and 12-20

Claims 1, 2, 5-10 and 12-20 are enabled.

The Examiner contends that the specification does not provide for the association of particular antigens or antibodies related to particular diseases. For example, it has been repeatedly stated by the Examiner during prosecution that "the specification does not associate any antigen (or antibody) with any particular disease with respect to presence (or absence) and amounts." The Examiner also contends that the specification fails to exemplify a correlation or statistically derived decision as to whether any test data set embraced by the claims can be associated with one or more of the diseases recited in the claims. The Examiner further contends that there is no guidance in the specification as to making a determination of or discovering unknown antibodies, and that more antibodies "would be required to be discovered, chosen or selected for includion in the method." It is respectfully submitted that the present invention involves neither associating particular antigens or antibodies with particular diseases nor determining or discovering unknown antibodies related to particular diseases.

Contrary to what has been stated by the Examiner, the presently claimed invention is not directed to, or concerned with, actively assigning presence, absence or amounts of any particular antibodies to any particular disease. Rather, the stored reference data sets are already associated with diseases as described, for example, in the specification at page 4, lines 15 to 29. In particular, the test subjects from which the references data sets are derived are known to either be disease free, or to have one or more specific SADs. This knowledge is reflected in the stored reference data sets themselves. Each reference data set is, *a priori*, associated with a particular known disease or with none. For example, as taught at page 4, lines 24 to 26, each reference data point is labeled as to the particular disease that is associated with its source sample. And from page 4, lines 11 to 15, each reference data set may be associated with a

specific disease or no disease. Also, each reference data set includes values for antibody levels based on the same antibody tests that were run on all the reference samples. The levels of the antibodies are those levels that are provided by the tests used, and the same or similar tests are used for both the test subject and the reference subjects. Thus, each stored reference data set includes, *a priori*, an association between a known disease (or none) and the levels of antibodies for which antibody testing was performed.

The invention resides in, and claim 1, for example, expressly recites, comparing a test data set and stored reference data sets which include 1) reference data sets obtained for each of the one or more systemic autoimmune diseases by subjecting biological samples of reference subjects, each known to have one of the one or more systemic autoimmune diseases, to said set of one or more tests, and 2) reference data sets obtained by subjecting biological samples of reference subjects known to not have one of the one or more systemic autoimmune diseases to said set of one or more tests. As taught at page 5, lines 1 to 5, for example, the test data set is based on a patient sample subjected to the same tests as were the reference samples. This is also clearly reflected in the claims wherein it is recited that the reference data sets are each obtained by subjecting a sample of a reference subject "to **said** set of one or more tests," (emphasis added) with said set of tests referring to the set of tests applied to the sample of the test subject. There is therefore no correlation between antibodies and diseases, but rather between one test data set and a plurality of reference data sets.

And there is no determination of unknown antibodies, nor is there a need for determining new antibodies; whichever antibody tests are decided to be used are used for both the reference data sets and the test data set. It is irrelevant for the purposes of the claimed invention which antibody tests and therefore also which antibodies are used for the tests, so long as there is some amount of consistency in the tests that are applied to the reference samples and the test sample to derive the data sets. The use of certain antibodies and certain antibody tests may lead to improved results (see, e.g., page 8, lines 9-12), however, the pending independent claims are not limited to the use of particular antibodies or antibody tests. Nor is the use of particular antibodies and antibody tests necessary; any antibodies and antibody tests known to

one skilled in the art may be used. For example, the Peter et al.[1] text referenced on page 7 of the specification shows that many autoimmune antibodies are known to exist and that a large number of these antibodies have known antigens. Further, it would be routine to one skilled in the art to identify additional antibodies that could be used with the present invention. For example, as specific antibodies are discovered, the tests to identify such antibodies *could* be used, but are certainly not required to be used, on reference samples as well as on the test sample so as to add an extra dimension to the N-dimensional data being processed according to the present invention. It is routine to one skilled in the art of antibody discovery to discover new antibodies as well as new techniques for such discovery. To those artisans, such matters of investigation are indeed routine, and are also outside the scope of the presently claimed invention.

The Examiner has also stated during prosecution that "the specification [does not] disclose how discrimination between different autoimmune diseases, particularly with those that involve overlapping autoantibodies, is to be implemented." (see, paper no. 10, page 6) To the contrary, the specification does indeed disclose how discrimination is achieved. Discrimination between the various autoimmune diseases is achieved by the KNN process as described in the specification, for example at the paragraph beginning on page 5, line 14. A disease that is associated with the k nearest (reference) data points is indicated as being present in the test sample, and if more than one disease is associated with the k nearest (reference) data points then an indication for each of the diseases (or none if the reference data points are associated with reference samples known to be disease free) is made. Additional refinements are also presented in the cited paragraph, such as, for example, to determine a confidence level of the diagnosis. Again, it is not particularly relevant which antibody tests are used, just that each of the data sets have been subjected to the same antibody testing. Once the indication has been made, a diagnosing physician, for example, may use the indication to assist with a diagnosis.

The Examiner has also contended that the specification provides no guidance on how to adapt known statistical pattern recognition means to solve the problem and that the specification does not address the difficulties in diagnosing autoimmune disorders based upon

[1] Peter et al. is cited only to indicate the state of the art, and is not a disclosure of the invention or of elements,

transient symptoms, overlapping symptoms, etc. To the contrary, as discussed above, the specification provides sufficient guidance to implement a KNN process, as is claimed, to provide a statistically derived decision. Further, the statistically derived decision itself helps a physician in overcoming such difficulties in diagnosing SADs in patients. The statistically derived decision can be used by the physician as an aid in diagnosis and/or to help determine whether further testing may be desired. Also, to the extent one skilled in the art would need to make assumptions as to what specific data would be used, such basic assumptions are a routine matter for one skilled in the art. For example, one skilled in the art would easily be able to implement commonly known data filtering, skew adjustment and normalization techniques as may be desired without undue experimentation, for example, where different test equipment is used for different samples. Certain assumptions made, and/or use of certain data modification techniques, could produce a more robust statistically derived decision, but the specification provides sufficient guidance for one skilled in the art to implement the claimed method, which provides a useful statistically derived decision.

Accordingly, it is respectfully asserted that the present specification provides sufficient guidance to enable one skilled in the art to make and use the claimed invention. Again, the presently claimed invention is directed to a method of processing data as recited therein. In particular, the specification fully supports and enables the claimed limitations of receiving a test data set, storing a plurality of reference data sets, comparing the test data set and the stored reference data sets by applying a KNN algorithm to produce a statistically derived decision whether the test subject is suffering from none, one or more SADs, and identifying which of the SADs the test subject is suffering from as is recited in claim 1, for example. It is noted that there is no recitation in the claims of discovering antibodies or of associating antibodies with particular diseases. Rather, each reference data set, *a priori*, includes an association with a disease (or none) based on the disease known to be afflicting the reference subject. Each reference data set also, *a priori*, includes an association with various antibodies by virtue of the antibody tests performed on the reference sample to produce the data set. Thus,

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otherwise unknown, that are critical or essential to the implementation of the invention.

each reference data set includes, *a priori*, an association between a known disease (or none) and the plurality of antibodies for which antibody testing was performed. Although the use of certain antibodies and certain antibody tests may lead to improved results, however, the invention and the pending independent claims are not limited to the use of particular antibodies or antibody tests.

Also, the specification supplies more than adequate support for one skilled in the art to implement a KNN algorithm using the data sets as recited in the claims. Further, the specification supplies more than adequate support for a useful structure and composition of the data sets themselves (e.g., training or reference data sets and test data set) for use in a KNN algorithm. Moreover, the training set and the test set include values for known (now or in the future) autoimmune antibodies. The specification explains this thoroughly and adequately, citing a large number of examples of autoimmune antibodies.

The specification is not a mere "invitation to experiment" as it is has been characterized in prior Office Actions. The specification is a teaching that when combined with the existing knowledge and the routine level of skill among data processors and statisticians provides a fully enabling disclosure to support the claims.

**CLAIMS APPENDIX**

1. (Previously Presented) A computer-implemented method of identifying whether a test subject is suffering from one or more systemic autoimmune diseases selected from the group consisting of systemic lupus erythmatosus, scleroderma, Sjögren's syndrome, polymyositis, dermatomyositis, CREST, and mixed connective tissue disease, said method comprising:

(a) receiving a test data set for the test subject, wherein the test data set is obtained by subjecting a biological sample of the test subject to a set of one or more tests that produce values representing levels of a plurality of autoaintibodies present in the sample such that the test data set has values representing levels of said plurality of autoantibodies;

(b) storing a plurality of reference data sets, including i) reference data sets obtained for each of said one or more systemic autoimmune diseases by subjecting biological samples of reference subjects, each known to have one of said one or more systemic autoimmune diseases, to said set of one or more tests, and ii) reference data sets obtained by subjecting biological samples of reference subjects known to not have one of said one or more systemic autoimmune diseases to said set of one or more tests, such that each stored reference data set has values representing levels of said plurality of autoantibodies, and wherein each stored reference data set is associated with none or one of said systemic autoimmune diseases;

(c) comparing the test data set and the stored reference data sets by applying a k-nearest neighbor algorithm to produce a statistically derived decision indicating whether the test subject is suffering from none, one or more of said systemic autoimmune diseases; and

(d) identifying which of said systemic autoimmune diseases the test subject is suffering from if the statistically derived decision indicates that the test subject is suffering from one or more of said systemic autoimmune diseases.

2. (Previously Presented) A method in accordance with claim 1 in which step (c) produces a statistically derived decision indicating whether said test subject is suffering from two of said systemic autoimmune diseases.

3. (canceled)

4. (canceled)

5. (Original) A method in accordance with claim 1 in which said plurality of autoantibodies numbers from 10 to 100 autoantibodies.

6. (Original) A method in accordance with claim 1 in which said plurality of autoantibodies numbers from 15 to 25 autoantibodies.

7. (Previously Presented) A method in accordance with claim 1 in which said plurality of autoantibodies comprises antibodies to at least fifteen of the following antigens:

SSA 60,
SSA 52,
SSB 48,
Sm BB',
Sm D1,
RNP 68,
RNP A,
RNP C,
Fibrillarin,
Riboproteins P0, P1, and P2,
dsDNA,
Nucleosome,
Ku,
Centromere A,

Centromere B,
Scl-70,
Pm-Scl,
RNA-Polymerases 1, 2, and 3,
Th,
Jo-1,
Mi-2,
PL7,
PL12, and
SRP.

8. (Previously Presented) A method in accordance with claim 1 in which said plurality of autoantibodies comprises antibodies to each of the following antigens:

SSA 60,
SSA 52,
SSB 48,
Sm BB',
Sm D1,
RNP 68,
RNP A,
RNP C,
Fibrillarin,
Riboproteins P0, P1, and P2,
dsDNA,
Nucleosome,
Ku,
Centromere A,
Centromere B,
Scl-70,

Pm-Scl,
RNA-Polymerases 1, 2, and 3,
Th,
Jo-1,
Mi-2,
PL7,
PL12, and
SRP.

9. (Previously presented) A method in accordance with claim 1 in which said reference data sets represent from 100 to 10,000 biological samples from reference subjects known to have systemic autoimmune diseases of known identity.

10. (Previously presented) A method in accordance with claim 1 in which said reference data sets represent from 200 to 2000 biological samples from reference subjects known to have systemic autoimmune diseases of known identity.

11. (canceled)

12. (Original) A method in accordance with claim 1 in which said biological sample from said test subject is a member selected from the group consisting of serum, plasma, urine, and cerebrospinal fluid.

13. (Original) A method in accordance with claim 1 in which said biological sample from said test subject is serum.

14. (Previously Presented) A method in accordance with claim 1 in which the one or more tests include a test based on analysis by immunoassay.

15. (Previously presented) A method in accordance with claim 1 in which the one or more tests include a test based on analysis by immunoassay with fluorescence detection.

16. (Previously presented) A method in accordance with claim 1 in which said one or more systemic autoimmune diseases includes systemic lupus erythmatosus.

17. (Previously Presented) A computer-implemented method of diagnosing whether a test subject is suffering from one or more systemic autoimmune diseases selected from the group consisting of systemic lupus erythmatosus, scleroderma, Sjögren's syndrome, polymyositis, dermatomyositis, CREST, and mixed connective tissue disease, said method comprising:

(a) receiving a test data set for the test subject, wherein the test d ata set includes data values obtained by analysis of a biological sample of the test subject and wherein the data values of the test data set represent levels of each of a plurality of autoantibodies;

(b) storing a plurality of reference data sets to a database, wherein the reference data sets include data values obtained by analysis of biological samples of reference subjects each known to have at least one of said one or more systemic autoimmune diseases, wherein the data values of each reference data set represent levels of each of said plurality of autoantibodies, and wherein each of the stored reference data sets is associated with one of said systemic autoimmune diseases; and

(c) applying a k-nearest neighbor algorithm to the test data set and the reference data sets from the database to produce a statistically derived decision indicating whether the test subject is suffering from one or more of said systemic autoimmune diseases, wherein the statistically derived decision includes an indication of one or more of said systemic autoimmune diseases.

18. (Previously Presented) The method of claim 17, wherein the autoantibody levels in the test and reference data sets are determined using the same multianalyte analysis tests.

19. (Previously Presented) The method of claim 17, wherein the data values obtained for each reference data set and the test data set are each determined in an automated test system.

20. (Previously Presented) The method of claim 1, wherein for the biological sample of the test subject the set of one or more tests are performed in an automated test system.

**EVIDENCE APPENDIX**

None

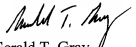
**RELATED PROCEEDINGS APPENDIX**

None

In view of the foregoing, Appellant respectfully requests consideration of the Appeal Brief and allowance of the pending claims.

Please deduct any requisite fees, pursuant to 37 CFR §1.17(C) and/or 37 CFR §§ 1.13(a) or 1.136(b) from deposit account 20-1430, and any additional fees associated with this Appeal Brief.

Respectfully submitted,



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